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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

JC882 U.S. PTO
09/634399
08/09/00

In Re Application of:

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Maw-Sheng Wu

Serial No.: Not assigned yet

Group Art Unit: Not assigned yet

Filing Date: August 9, 2000

Examiner: Not assigned yet

For: NOVEL COMPOSITIONS OF MINOXIDIL

EXPRESS MAIL LABEL NO: EL568026557US
DATE OF DEPOSIT: August 9, 2000

- Box Patent Application
- Provisional Design

Assistant Commissioner for Patents
Washington DC 20231

Sir:

PATENT APPLICATION TRANSMITTAL LETTER

Transmitted herewith for filing, please find

- A Utility Patent Application under 37 C.F.R. 1.53(b).

It is a continuing application, as follows:

- continuation divisional continuation-in-part of prior application number
____/____.

- A Provisional Patent Application under 37 C.F.R. 1.53(c).
- A Design Patent Application (submitted in duplicate).

Including the following:

08/60/80 " 568026557US "

Provisional Application Cover Sheet.

New or Revised Specification, including pages 1 to 36 containing:

Specification

Claims

Abstract

Substitute Specification, including Claims and Abstract.

The present application is a continuation application of Application No. _____ filed _____. The present application includes the Specification of the parent application which has been revised in accordance with the amendments filed in the parent application. Since none of those amendments incorporate new matter into the parent application, the present revised Specification also does not include new matter.

The present application is a continuation application of Application No. _____ filed _____, which in turn is a continuation-in-part of Application No. _____ filed _____. The present application includes the Specification of the parent application which has been revised in accordance with the amendments filed in the parent application. Although the amendments in the parent C-I-P application may have incorporated new matter, since those are the only revisions included in the present application, the present application includes no new matter in relation to the parent application.

A copy of earlier application Serial No. _____ Filed _____, including Specification, Claims and Abstract (pages 1 - @@), to which no new matter has been added TOGETHER WITH a copy of the executed oath or declaration for such earlier application and all drawings and appendices. Such earlier application is hereby incorporated into the present application by reference.

Please enter the following amendment to the Specification under the Cross-Reference to Related Applications section (or create such a section) : "This Application:
 is a continuation of is a divisional of claims benefit of U.S. provisional Application Serial No. _____ filed _____

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- Signed Statement attached deleting inventor(s) named in the prior application.
- A Preliminary Amendment.
- _____ Sheets of Formal Informal Drawings.
- Petition to Accept Photographic Drawings.
- Petition Fee
- An Executed Unexecuted Declaration or Oath and Power of Attorney.
- An Associate Power of Attorney.
- An Executed Copy of Executed Assignment of the Invention to _____

 - A Recordation Form Cover Sheet.
 - Recordation Fee - \$40.00.
- The prior application is assigned of record to _____
- Priority is claimed under 35 U.S.C. § 119 of Patent Application No. _____
filed _____ in _____ (country).
 - A Certified Copy of each of the above applications for which priority is claimed:
 - is enclosed.
 - has been filed in prior application Serial No. _____ filed _____.
- An Executed or Copy of Executed Earlier Statement Claiming Small Entity Status under 37 C.F.R. 1.9 and 1.27
 - is enclosed.
 - has been filed in prior application Serial No. _____ filed _____, said status is still proper and desired in present case.
- Diskette Containing DNA/Amino Acid Sequence Information.

ORIGINAL ATTACHED

- Statement to Support Submission of DNA/Amino Acid Sequence Information.

- The computer readable form in this application _____, is identical with that filed in Application Serial Number _____, filed _____. In accordance with 37 CFR 1.821(e), please use the first-filed, last-filed or only computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the computer readable form that will be used for the instant application. A paper copy of the Sequence Listing is included in the originally-filed specification of the instant application, included in a separately filed preliminary amendment for incorporation into the specification.

- Information Disclosure Statement.
 - Attached Form 1449.
 - Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith.

- A copy of Petition for Extension of Time as filed in the prior case.

- Appended Material as follows: _____ .

- Return Receipt Postcard (should be specifically itemized).

- Other as follows: _____

_____ .

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FEE CALCULATION:

- Cancel in this application original claims _____ of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

			SMALL ENTITY		NOT SMALL ENTITY	
			RATE	FEE	RATE	FEE
PROVISIONAL APPLICATION			\$75.00	\$	\$150.00	\$
DESIGN APPLICATION			\$155.00	\$	\$310.00	\$
UTILITY APPLICATIONS BASE FEE			\$345.00	\$	\$690.00	\$ 690.00
UTILITY APPLICATION; ALL CLAIMS CALCULATED AFTER ENTRY OF ALL AMENDMENTS						
		No. Filed	No. Extra			
TOTAL CLAIMS		118 - 20 =	98	\$9 each	\$	\$18 each \$ 1764.00
INDEP. CLAIMS		6 - 3 =	3	\$39 each	\$	\$78 each \$ 234.00
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM			\$130	\$	\$260	\$
ADDITIONAL FILING FEE						
TOTAL FILING FEE DUE					\$ 2,688.00	

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- A Check is enclosed in the amount of \$ 2,688.00.
- The Commissioner is authorized to charge payment of the following fees and to refund any overpayment associated with this communication or during the pendency of this application to deposit account 23-3050. This sheet is provided in duplicate.
 - The foregoing amount due.
 - Any additional filing fees required, including fees for the presentation of extra claims under 37 C.F.R. 1.16.
 - Any additional patent application processing fees under 37 C.F.R. 1.17 or 1.20(d).
 - The issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance.
- The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-

identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

SHOULD ANY DEFICIENCIES APPEAR with respect to this application, including deficiencies in payment of fees, missing parts of the application or otherwise, the United States Patent and Trademark Office is respectfully requested to promptly notify the undersigned.

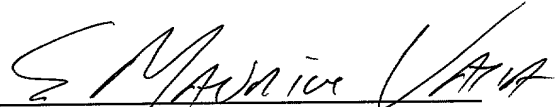
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NOVEL COMPOSITIONS OF MINOXIDIL**Field of the Invention**

5 The present invention relates to novel compositions of minoxidil, methods for making the compositions, and methods for inducing and/or stimulating hair growth and/or reducing hair loss using the compositions.

Background of the Invention

10 Minoxidil (*i.e.*, 2,4-diamino-6-piperidinylpyrimidine-3-oxide) is the active ingredient of Loniten® and Rogaine®, which are marketed by Pharmacia & Upjohn as a treatment for hypertension, and as a treatment and preventative for androgenic alopecia (male and female pattern baldness), respectively. The preparation and antihypertensive use of minoxidil is described in U.S. Patent. No. 3,461,461. Methods and topical preparations for using the compound to grow hair and to treat male and female pattern baldness are described and claimed in U.S. Patents Nos. 4,139,619 and 4,596,812.

15 Pharmaceutical compositions for topical application, such as Rogaine®, may take a variety of forms including, for example, solutions, gels, suspensions, and the like. Generally speaking, improved absorption may be achieved when the topical compositions are in the form of a solution or gel, *i.e.*, where the active ingredient, for example, minoxidil, is dissolved in the carrier solution, in contrast to topical compositions which are in the form of suspensions, *i.e.*,
20 where the active ingredient is merely suspended in the composition.

Solutions of minoxidil typically contain water and one or more additional solvents. Topical solutions have not been entirely satisfactory for use in treating the scalp, however, as they tend not to remain in place long enough for satisfactory amounts of the drug to be absorbed. Formulations of minoxidil, such as jellies and ointments, have also been proposed.

5 These compositions may not be pharmaceutically elegant, and also may not be suitable for use as treatments for stimulating the growth of hair, especially from a cosmetic point of view.

The use of polymeric thickening agents as part of the delivery vehicle for minoxidil, has also been described. GB 2 194 887, for example, describes a preparation containing a polymer, up to 20% solvent (i.e. propylene glycol), and up to 5% minoxidil. This application teaches that at least a part of the minoxidil may be in the form of micronized particles suspended in the delivery medium, however, rather than in solution. U.S. Patent No. 5,225,189

10 also describes preparations containing a carbomeric polymer, and provides examples of single-phase gel preparations having up to 3% solubilized minoxidil therein.

Attempts to provide pharmaceutically appropriate thickened formulations containing higher concentrations of solubilized minoxidil are hampered, however, by various processing difficulties. For example, minoxidil is poorly soluble, and may precipitate out of solution by the addition of additional ingredients, such as thickening agents. Accordingly, high percentages of solvents, such as propylene glycol and alcohol, may be required. Frequently, however, these high solvent percentages may be incompatible with many pharmaceutical

15 additives, such as thickening agents, and may generally result in a pharmaceutically inelegant product. Carbopol® 934P, for example, the carbomer polymer used in the examples of U.S. Patent No. 5,225,189, in the presence of high percentages of solvent and inadequate amounts of water, affords a thick, doughy mass that may be unworkable with equipment commonly employed to manufacture pharmaceutical products.

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25 There remains a need for new pharmaceutically elegant compositions of minoxidil which can be prepared using the equipment and techniques commonly used for the large scale, commercial production of topical pharmaceutical preparations. The present invention is directed to these, as well as other, important ends.

Summary of the Invention

The present invention is directed, in part, to novel compositions of minoxidil. Specifically, in one embodiment, there is provided a composition comprising minoxidil, a non-carbomeric thickening agent, and a pharmaceutically acceptable solvent, wherein the minoxidil is substantially solubilized in said composition.

Another embodiment of the invention relates to a composition comprising greater than 3% minoxidil, a solvent-tolerant carbomer, and a pharmaceutically acceptable solvent, wherein said minoxidil is substantially solubilized in said composition.

Yet another embodiment of the invention relates to a composition comprising:

from greater than about 3% to about 8% of minoxidil;
from about 30% to about 80% of a polyol;
from about 10% to about 50% of an alcohol;
from about 0.01% to about 50% of a non-carbomeric polymer;
from about 0% to about 3% of a neutralizing agent; and
water (qs); wherein said minoxidil is substantially solubilized in said

composition.

Still another embodiment of the invention relates to a non-gelled composition comprising minoxidil, a thickening agent, and a pharmaceutically acceptable solvent, wherein said minoxidil is substantially solubilized in said composition.

Another embodiment of the invention relates to a process for preparing a composition comprising:

from greater than about 3% to about 8% of minoxidil;
from about 30% to about 80% of a polyol;
from about 10% to about 50% of an alcohol;
from about 0.01% to about 50% of a non-carbomeric polymer;
from about 0% to about 3% of a neutralizing agent; and
water (qs); wherein said minoxidil is substantially solubilized in said

composition, said process comprising:

(a) providing a solution comprising said minoxidil, said polyol, a portion of said alcohol, and a substantial majority of said neutralizing agent;

- (b) providing a dispersion comprising said polymeric thickening agent, the remaining portion of said alcohol, any remainder of said neutralizing agent and said water; and
- (c) combining said solution and said dispersion to provide the gel composition.

5 Still another aspect of the invention relates to a process for preparing a non-gelled composition comprising minoxidil, a thickening agent, a pharmaceutically acceptable solvent, and water, wherein the minoxidil is substantially solubilized in the non-gelled composition, and wherein the process comprises combining together the minoxidil, thickening agent,
10 pharmaceutically acceptable solvent and water to provide the composition.

Methods for treating and/or preventing hair loss in a region of a patient, wherein the methods comprise topically administering to the region compositions as described herein, are also provided by the present invention.

15 These and other aspects of the invention will become more apparent from the present disclosure and claims.

Detailed Description of the Invention

The present invention is directed, in part, to novel compositions of minoxidil (*i.e.*, 2,4-diamino-6-piperidinylpyrimidine-3-oxide) and their use in the treatment and/or prevention of hair loss. As noted above, the preparation and antihypertensive use of minoxidil is described in
20 U.S. Patent. No. 3,461,461, and topical preparations and methods relating to the use of the compound to grow hair and to treat androgenic alopecia are described and claimed in U.S. Patents No. 4,139,619 and 4,596,812. The disclosures of these three patents are hereby incorporated herein by reference, in their entireties.

25 The compositions of the present invention may take a variety of forms including, for example, gelled compositions and non-gelled compositions. The terms "gel" and "gelled composition", as used herein, refer to colloidal compositions which are preferably semisolid systems that may be composed of suspensions made up of small inorganic particles, or may comprise large organic molecules interpenetrated by a liquid. The term "non-gelled," as used herein, refers to compositions of the present invention which are not in the form of gels.

30 Examples of non-gelled compositions include, for example, emulsions, thickened solutions, and

the like. The term "thickened", as used herein, refers to compositions in which the viscosity has been enhanced to a viscosity greater than about that of water at ambient room temperature. The term "emulsion", as used herein, refers to a mixture of two or more liquids which may be in the form of a continuous phase and a disperse phase, for example. Exemplary emulsions may be in the form of creams or lotions, for example, and may include, for example, oil-in-water emulsions, water-in-oil emulsions, multiple emulsions and microemulsions. The term "suspension", as used

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In preferred embodiments, the compositions of the present invention may be gels, with single-phase gels being more preferred. The term "single-phase gel", as used herein, refers to gels that may comprise organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from synthetic macromolecules (*e.g.*, acrylic acid polymers) or from natural gums (*e.g.*, Tragacanth).

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The viscosity of the compositions of the present invention may vary and may depend, for example, on whether the compositions are gelled compositions or non-gelled compositions. In the case of gels, the compositions may have a viscosity at ambient room temperature which generally ranges from greater than about 4,000 centipoise to about 5 million centipoise, and all combinations and subcombinations of ranges and specific viscosities therein. More preferably, the gel compositions of the present invention may have a viscosity of from about 5,000 centipoise to about 50,000 centipoise, with viscosities of from about 6,000 centipoise to about 25,000 centipoise being even more preferred. In the case of non-gelled compositions, the compositions may have a viscosity at ambient room temperature which generally ranges from greater than about 6 centipoise to about 4,000 centipoise, and all combinations and subcombinations of ranges and specific viscosities therein. More preferably, the non-gelled compositions of the present invention may have a viscosity of from about 50 centipoise to about 3,000 centipoise, with viscosities of from about 100 centipoise to about 2,000 centipoise being even more preferred.

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The concentration of the minoxidil in the present compositions may vary and may depend, for example, on the particular form of the composition, for example, whether the compositions are gelled compositions or non-gelled compositions. Broadly speaking, the minoxidil may be present in the present composition in an amount which ranges from greater

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than about 0.01% to about 8%, and all combinations and subcombinations of ranges and specific amounts therein. As used herein, the term "%" refers to weight %, unless otherwise indicated. In addition, the total % of components in the present compositions may not exceed 100%. In preferred embodiments, the minoxidil may be present in a concentration of greater than about 5 3%, with concentrations of greater than about 3% to about 8% being more preferred. In other preferred embodiments, concentrations of greater than 3% are preferred, with concentrations of from greater than 3% to about 8% being more preferred. In the case of certain preferred compositions, including certain gel compositions, the minoxidil may be present in a concentration of from about 4% to about 8%, about 5% to about 8%, about 6% to about 8% and 10 about 7% to about 8%. In even more preferred embodiments, the minoxidil may be present in an amount of from about 4% to about 7%, or about 5% to about 6%, with concentrations of about 5% being particularly preferred.

The compositions of the present invention further preferably comprise a pharmaceutically acceptable solvent, and in preferred form, the minoxidil may be substantially 15 solubilized therein. The term "substantially solubilized", as used herein, means that the minoxidil is dissolved in the compositions and is present at a concentration which is less than about its solubility limit in the present compositions. The term "pharmaceutically acceptable", as used herein, refers to materials which are generally not toxic or injurious to a patient when used in the compositions of the present invention, including when the compositions are applied topically 20 according to methods described herein. The term "patient", as used herein, refers to animals, including mammals, preferably humans.

A wide variety of solvents may be used in the compositions of the present invention. Preferably, the solvent is a polar solvent. Preferred among these are polar, protic solvents. Preferably, the solvent is a hydroxy compound, *i.e.*, a compound containing at least one 25 hydroxy (OH) group. Preferred among the hydroxy compounds are alcohols (*i.e.*, compounds containing one hydroxy group) or polyols (*i.e.*, compounds containing two or more hydroxy groups) or mixtures of alcohols and/or polyols. Exemplary alcohols include, for example, , ethanol, propanol and butanol. Reference herein to "ethanol" includes absolute alcohol, as well as "alcohol USP" and all denatured forms of 95% ethanol. As used herein, the term "propanol" 30 refers to all isomeric forms, including n-propanol and isopropanol, and the term "butanol" refers to all isomeric forms, including, for example, n-butanol, iso-butanol and sec-butanol. Preferred

among these alcohols are ethanol and propanol, with ethanol being more preferred. Exemplary polyols include, for example propylene glycol, dipropylene glycol, hexylene glycol, 1,3-butylene glycol, liquid polyethylene glycols, such as polyethylene glycol 200 (PEG-200) and polyethylene glycol 400 (PEG-400), and glycerol (the latter also referred to sometimes as glycerine). Preferred
5 among these polyols is propylene glycol. In a particularly preferred embodiment, the solvent employed may be a mixture of an alcohol and a polyol.

The amount of solvent employed in the compositions of the present invention may vary and will depend, for example, on the particular solvent and thickening agent employed, the quantity of minoxidil employed, and the like. Preferably, the solvent may be employed in a
10 quantity sufficient to assure that the minoxidil is solubilized in the present compositions. Preferably, the solvent may be employed in the present compositions in an amount ranging from about 1% to about 99%, and all combinations and subcombinations of ranges and specific amounts therein. More preferably, the solvent may be employed in an amount of at least about
15 20%. Even more preferably, the solvent may be employed in the present compositions in an amount of from about 20% to about 99%, with concentrations of from about 30 to about 80% being yet more preferred.

Preferably, the present compositions may comprise from about 30% to about 80% of a polyol and from about 10% to about 50% of an alcohol. More preferably, the present compositions may comprise from about 40% to about 70% of a polyol and from about 20% to
20 about 30% of an alcohol. Even more preferably, the present compositions may comprise from about 50% to about 60% of a polyol and from about 25% to about 30% of an alcohol. Even more preferably, the present compositions may comprise about 53% of a polyol and about 26% of an alcohol.

Also in preferred form, the ratio of solvent to minoxidil in the present
25 compositions is about 10:1. Ratios described herein are weight:weight ratios. Preferably, the ratio of solvent to minoxidil in the present compositions is about 12:1, with a ratio of about 15:1 being more preferred. Also in preferred form, the ratio of polyol to minoxidil in the present compositions is at least about 5:1. Preferably, the ratio of polyol to minoxidil in the present compositions is at least about 8:1, with a ratio of about 10:1 being more preferred. Further in
30 preferred form, the ratio of alcohol to minoxidil in the present compositions is at least about 3:1.

Preferably, the ratio of alcohol to minoxidil in the present compositions is at least about 4:1, with a ratio of about 5:1 being more preferred.

In accordance with preferred embodiments of the invention, the enhanced viscosities of the present compositions may be achieved through the use of thickening agents.

5 The term "thickening agent", as used herein, refers to any of a variety of generally hydrophilic materials which, when incorporated in the present compositions, may act as viscosity modifying agents, emulsifying agents, gelling agents, suspending agents, and/or stabilizing agents. It is contemplated that the thickening agents may be capable of aiding in maintaining the stability of the compositions due to such properties. If desired, two or more thickening agents may be
10 employed in the present compositions.

A wide variety of thickening agents are known to those skilled in the art and may be used in the practice of the present invention. In preferred embodiments, the thickening agent may be an organic thickening agent or an inorganic thickening agent, with organic thickening agents being more preferred. Preferred among the organic thickening agents are polymeric
15 thickening agents. The term "polymer", as used herein, refers to molecules formed from the chemical union of two or more units. Accordingly, included within the term "polymer" are, for example, dimers, trimers and oligomers. The polymer may be synthetic, naturally-occurring or semisynthetic. In preferred form, the term "polymer" refers to molecules which comprise 10 or more repeating units. Suitable polymeric thickening agents for use in the present compositions
20 include, for example, starches, gums, pectin, casein, gelatin, phycocolloids and synthetic polymers. Exemplary of the foregoing materials are, for example, alginates and salts and derivatives thereof, including, for example, sodium alginate and propylene glycol alginate, acacia, carrageenan, guar gum, karaya gum, locust bean gum, tragacanth, xanthan gum, celluloses and salts and derivatives thereof including, for example, carboxymethylcellulose,
25 carboxymethylcellulose sodium, carboxymethylcellulose calcium, ethylcellulose, hydroxyethylcellulose, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose and powdered cellulose, hyaluronic acid and salts thereof such as, for example, sodium hyaluronate, gelatin and polydextrose.

Other polymeric thickening agents which may be employed include, for example,
30 polymers of acrylic acid, such as crosslinked homopolymers of acrylic acid, crosslinked copolymers of acrylic acid, crosslinked interpolymers of acrylic acids, polyacrylic acid and salts

thereof, acrylic/acrylate copolymers, dimethicone copolyols, polyacrylamide, ethylene/sodium acrylate copolymer, acrylamide/sodium acrylate copolymer, sodium acrylate/vinyl alcohol copolymer, sodium polymethacrylate, sodium polystyrene sulfonate, povidone and derivatives thereof, polyquaternium compounds, such as polyquaternium10, polyvinyl alcohol, polyethylene oxide and poloxamers.

Any of the foregoing thickening agents may be employed in the compositions of the present invention. In certain preferred embodiments, the thickening agent may be a non-carbomeric thickening agent. The term "carbomer", as defined by the Cosmetics, Toiletry and Fragrance Association (CTFA), and as used herein, refers to synthetic, high molecular weight crosslinked homopolymers of acrylic acid. Examples of carbomers include, for example, Carbopols, such as Carbopol® 934P, Carbopol® 940, Carbopol® 980, Carbopol® 981 and Carbopol® Ultrez™ 10, commercially available from B.F. Goodrich (Cleveland, OH). The term "non-carbomeric", as used herein, refers to thickening agents that are not carbomers.

Certain carbomers are particularly useful in compositions which contain higher amounts of solvent, for example, protic solvents, such as alcohols and polyols, and lower amounts of water. Such carbomers are referred to herein as "solvent-tolerant carbomers," and include such carbomers as, for example, Carbopol® Ultrez™ 10 and Carbopol® 940, 941, 980 and 981 (all commercially available from B.F. Goodrich). In high solvent/low water compositions, such as those containing, for example, greater than about 50% solvent and/or less than about 25% water, these solvent-tolerant carbomers may be especially useful as viscosity modifying agents, *i.e.*, they can be advantageously used to emulsify, gel, suspend, and/or stabilize the compositions. In contrast, other carbomers are not particularly adaptable to modifying the viscosities of high solvent/low water compositions, but are more advantageously employed in compositions containing lower amounts of solvent and/or higher amounts of water. Such carbomers which are not particularly useful in high solvent/low water compositions include, for example, Carbopol® 934P. Thus, for example, Carbopol® 934P is not a solvent-tolerant carbomer within the context of the present invention, and is not suitable for embodiments of the present invention that are characterized as being high solvent/low water compositions.

In the case of gel compositions, preferred thickening agents are copolymers of acrylic acid, with crosslinked copolymers of acrylic acid being more preferred. Particularly preferred among these thickening agents are acrylate/C₁₀₋₃₀ alkyl acrylate crosspolymers.

Examples of acrylate/C₁₀₋₃₀ alkyl acrylate crosspolymers that may be suitable for use in the present compositions are Pemulen® polymeric emulsifiers, including Pemulen® TR 1 and Pemulen® TR 2, commercially available from B.F. Goodrich (Cleveland, OH).

In an alternate preferred embodiment of the present invention, the present
5 compositions may comprise inorganic thickening agents. Suitable inorganic thickening agents include, for example, bentonite, magnesium aluminum silicate and colloidal silicon dioxide.

The amount of thickening agent employed in the present compositions may vary and depends, for example, on the particular polymer and solvent employed, the quantity of minoxidil, the desired viscosity of the final composition and the like. Generally speaking, the
10 thickening agent may be employed in an amount to provide the compositions with a desired viscosity. Preferably, the thickening agent may be employed in an amount which ranges from about 0.01% to about 50%, and all combinations and subcombinations of ranges and specific amounts therein. More preferably, the thickening agent may be employed in an amount of from about 0.1% to about 3%, with from about 0.15% to about 0.6% being even more preferred.

The compositions of the present invention may further comprise one or more
15 neutralizing agents, which may be used to adjust the pH of the compositions. The term "neutralizing agent", as used herein, refers to a material that may be used to modify the pH of the present compositions, for example, from an acidic pH to a more basic pH, or from a basic pH to a more acidic pH. Components of the present compositions, such as certain of the thickening
20 agents, may be acidic, and may be preferably neutralized to achieve the desired thickening effect. Accordingly, the neutralizing agents are preferably those materials which may be used to modify the pH of the present compositions from an acidic pH to a more basic pH.

A wide variety of neutralizing agents are known to those skilled in the art and may
25 be used in the practice of the present invention. Exemplary neutralizing agents include, for example, ammonium hydroxide, arginine, 2-amino-2-methyl-1-propanol (AMP-95® (Angus)), dimethanolamine, dibutanolamine, diisobutanolamine, tributanolamine, triisobutanolamine, tri-sec-butanolamine, tripropylamine, ethanolamine, diethanolamine, triethanolamine, PEG-15 cocamine, diisopropanolamine, methylethanolamine, diisopropylamine, dipropylenetriamine, tromethamine, isopropylamine ethylene diamine, triisopropanolamine, tetrahydroxypropyl
30 ethylenediamine, trimethamine, 2-aminobutanol, aminoethyl propanediol, aminomethyl

propanediol, aminomethyl propanol, sodium hydroxide, potassium hydroxide and mixtures thereof.

Preferably, the neutralizing agent is selected from 2-amino-2-methyl-1-propanol, diisopropanolamine, triisopropanolamine and tetrahydroxypropyl ethylenediamine, and mixtures thereof. More preferably, the neutralizing agent is 2-amino-2-methyl-1-propanol.

The amount of neutralizing agent employed in the compositions of the present invention may vary and will depend, for example, on the particular neutralizing and thickening agents employed, the quantity of thickening agent to be neutralized, the desired pH of the compositions, and the like. Preferably, the neutralizing agent may be employed in the present compositions in an amount which ranges from about 0% to about 5% (and all combinations and subcombinations of ranges and specific amounts therein), based on the total weight of the composition. More preferably, the neutralizing agent may be employed in the present compositions in an amount of from about 0% to about 3%. Even more preferably, the neutralizing agent may be employed in the present compositions in an amount of from about 0.03% to about 1%, with concentrations of from about 0.15% to about 0.6% being still more preferred.

The quantity of neutralizing agent used may also be expressed in terms of the ratio of thickening agent to neutralizing agent. Ratios described herein are weight:weight ratios. Preferably, the ratio of thickening agent to neutralizing agent is from about 10:1 to about 1:6, and all combinations and subcombinations of ranges and specific ratios therein. More preferably, the ratio of thickening agent to neutralizing agent is from about 2:1 to about 1:2, with a ratio of about 10:6 being even more preferred.

In addition to minoxidil, thickening agent and pharmaceutically acceptable solvent, the compositions of the present invention may further preferably comprise water. It has been found that desirable pharmaceutically elegant characteristics may be achieved by including water in the present compositions. The term "pharmaceutically elegant", as used herein, means that the compositions are preferably smooth, and not gritty or greasy to the touch. Preferably, water may be included in the present compositions in an amount of no greater than about 80%. More preferably, water may be employed in the present compositions in an amount which may range from about 0.1% to about 70%, and all combinations and subcombinations of ranges and specific amounts therein. Still more preferably, the water may be employed in the present

compositions in an amount of from about 10% to about 25%, with amounts of from about 14% to about 16% being yet more preferred.

The compositions of the present invention may be topically administered to a region of a patient for the prevention or treatment of hair loss. Accordingly, as would be
5 apparent to one of skill in the art, once armed with the teachings of the present disclosure, the compositions may optionally comprise additional pharmaceutically acceptable additives and ingredients such as, for example, hair conditioners, such as vitamin B5/panthenol, calcium pantothenate or other panthenol derivatives, colorants, fragrances, fragrance modifiers, other
10 vitamins such as vitamin E, penetration modifiers, such as azone and DEET, surfactants, such as Cremophor® (BASF), cosmetic agents for the skin or scalp, such as fatty acids and fatty acid esters, herbal extracts, such as henna, other viscosity enhancing or thickening agents, oils, emulsifiers, wetting agents, sunscreens and anti-irritants.

A wide variety of methods may be used for preparing the compositions of the present invention. Broadly speaking, the compositions may be prepared by combining together
15 the components of the compositions, as described herein, at a temperature and for a time sufficient to preferably provide a pharmaceutically elegant composition. The term "combining together", as used herein, means that all of the components of the compositions may be combined and mixed together at about the same time. For example, non-gelled compositions, including non-gelled compositions comprising minoxidil, a thickening agent, a pharmaceutically acceptable
20 solvent, and water, may be prepared by combining together the minoxidil, thickening agent, pharmaceutically acceptable solvent and water to provide the non-gelled composition. In certain preferred embodiments, the term "combining together" means that the various components may be combined in one or more preferential sequences to provide the desired product.

In methods for forming non-gelled compositions, the water and thickening agent
25 may preferably be combined together to produce a uniformly dispersed and hydrated mixture. To this can be added the solvent, and optionally, any neutralizing agent may be added. The minoxidil may then be added to the mixture, which may then be blended until the minoxidil is dissolved. Alternatively, the minoxidil may be first dissolved in the solvent, and then this mixture may be added to the mixture of the thickening agent and water.

30 Attempts to form pharmaceutically elegant polymeric gels of minoxidil by conventional means have in the past been hampered by processing difficulties, including (1) the

poor solubility of minoxidil, (2) difficulties in obtaining effective and efficient dispersion of the thickening agent and maintenance of polymer solution; and (3) precipitation of the minoxidil. These problems are often exacerbated when using higher concentrations of minoxidil. For example, the use of higher amounts of minoxidil may require correspondingly higher amounts of solvent. However, the use of higher amounts of solvents results in the use of water in amounts that may be insufficient to provide a suitable dispersion of the thickening agent. On the other hand, the use of higher amounts of water may cause the minoxidil to precipitate.

In addition, conventional techniques for preparing gel formulations of a drug, which may involve, for example, the sequential mixing of a solvent, a thickening agent, a drug, and a neutralizing agent, have proven unsatisfactory in the case of gel formulations of minoxidil in that the combination of the components in the conventional manner results in the formation of a white precipitate. Analysis of this precipitate indicates the presence of both thickening agent and minoxidil.

It has been surprisingly and unexpectedly found, however, that a pharmaceutically elegant polymeric gel composition of the present invention, including gels comprising from greater than 3% to about 8% minoxidil, from about 30% to about 80% of a polyol; from about 10% to about 50% of an alcohol, from about 0.01% to about 3% of a non-carbomeric polymer, from about 0% to about 3% of a neutralizing agent, and a sufficient quantity of water can be conveniently and effectively produced by the methods disclosed herein. In preferred form, the method may comprise providing a solution comprising minoxidil, a pharmaceutically acceptable polyol, a portion of the alcohol and the neutralizing agent (step a). The method further preferably comprises providing a dispersion comprising the thickening agent, the remaining portion of the alcohol, and the water (step b). Both the solution and dispersion may be obtained, for example, by combining together the various components of the solution and dispersion, respectively. The solution and the dispersion may then be combined until a uniform gel composition is produced (step c).

Depending upon the thickening agent chosen, it may be possible to add all of the alcohol to the dispersion of step (b), rather than adding a portion of the alcohol to the minoxidil solution of step (a). Some thickening agents may not tolerate the high alcohol/low water environment, however, or will not produce a satisfactory or workable dispersion. Additionally, it has been found that the addition of some of the alcohol to the solution of step (a) may promote

dissolution of the minoxidil in the polyol, and may, for example, avoid the necessity of heating the solution and permit step (a) to be performed at room temperature. Thus it is preferable that about 50% of the alcohol is used in the solution of step (a), and the remaining 50% is used in the dispersion of step (b).

5 A substantial majority of any neutralizing agent is preferably included in the solution of step (a), although a small percentage of the total amount of neutralizing agent may be included in the dispersion of step (b). As used herein, the term “substantial majority” refers to greater than about 80% of the total amount of the neutralizing agent, with greater than about 90% being preferred. Embodiments of the process wherein the neutralizing agent is substantially
10 completely added to the solution of step (a) are even more preferred. As used herein, the term “substantially completely” means greater than about 99% of the total amount of neutralizing agent.

The compositions of the present invention may be advantageously employed to treat and/or prevent a region of hair loss or alopecia in a patient. Generally speaking, the
15 methods may comprise topically administering to the region a composition as described herein. The life of a hair is subjected to a cycle, called the pilar cycle, during which the hair grows (anagen), transitions (catagen), and falls out (telogen), before being replaced by a new hair which appears in the same follicle and the cycle is repeated. This constant renewal process undergoes a natural change during ageing. The hair cycles become shorter, resulting in finer, shorter hairs.
20 Hair loss results when this process is accelerated or disturbed, i.e. the growth phases become shorter, the passage of hair into the telogen phase is earlier and hairs fall out in larger numbers. Successive shortening growth cycles may result in increasingly fine and short hair, which is slowly converted into fluff. This phenomenon may lead to progressive hair thinning and may eventually lead to baldness.

25 Dermatologists recognize many different types of hair loss, the most common by far being androgenic alopecia (also known as “pattern baldness”), wherein humans begin losing scalp hair as they get older. While this type of hair loss is more common in males, it also occurs in women. This type of alopecia may be characterized by progressive thinning, as discussed above, or may be characterized by hair loss with little diffuse hair thinning, such as frontal hair
30 loss, mid-anterior balding, bitemporal recession, and/or vertex balding. Alopecia areata, anagen hair loss, and diffuse alopecia, such as telogen effluvium are other presentations of hair loss,

which may be distinguished from androgenic alopecia. These other forms of hair loss may also be treated with topical minoxidil.

The invention is further described in the following examples. All of these examples are actual examples. These examples are for illustrative purposes only, and are not to be construed as limiting the appended claims.

Example I

A gel composition within the scope of the present invention and containing 5% minoxidil was prepared as follows:

Part I Solution

10	Minoxidil USP	50.7 mg
	Propylene Glycol USP	526 mg
	Alcohol USP	130 mg
	AMP-95® (2-amino- 2-methyl-1-propanol)	1.5 mg

Part II Dispersion

15	Pemulen® TR-1 NF	2.5 mg
	Purified Water USP	153 mg
	Alcohol USP	136.3 mg

Procedure

20 The alcohol and propylene glycol in Part I were mixed together, and the minoxidil was dissolved in the resulting solvent mixture. AMP-95® was added to the solution and mixed until dissolved. The alcohol and water in Part II were combined. The Pemulen® was gradually mixed into the alcohol/water mixture, until a uniform dispersion was produced. The Part I solution was then gradually added to the Part II dispersion with constant mixing, until a uniform
25 gel developed. The resulting gel had a very nice appearance, with a smooth consistency, excellent clarity and a moderate viscosity.

Example II

A minoxidil gel was prepared as described in Example I, except none of the alcohol was used in the Part I solution. It was necessary to heat the propylene glycol to dissolve the minoxidil, which remained in solution upon cooling to room temperature. The alcohol was then added to the solution, and the gel prepared, as in Example I. This example shows that mixing the alcohol and propylene glycol together prior to adding the minoxidil avoids the need for heating the solution to dissolve the minoxidil.

Example III

A 5% minoxidil gel was prepared as follows:

Part I Solution

Minoxidil USP	22.14 mg
Propylene Glycol USP	526 mg

Part II Dispersion

Pemulen® TR-1 NF	5 mg
Purified Water USP	153 mg
Alcohol USP	260.7 mg

Part III Neutralizer

AMP-95® (2-amino-2-methyl-1-propanol)	5 mg
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Procedure

The propylene glycol and minoxidil were mixed together and heated to dissolve the minoxidil as in Example II. The alcohol and water from Part II were mixed and the minoxidil solution from Part I was added and mixed until uniform. The Pemulen® was gradually added to the minoxidil solution formed by combining Parts I and II. Upon initiating addition of the Pemulen® to the minoxidil solution, the mixture began forming a gel. Continued addition of Pemulen® resulted in a non-uniform mixture of non-dispersed small clumps of Pemulen® in the dry state and "fish eyes" (i.e. individual, partially hydrated gelatinous masses of Pemulen®).

Continued mixing resolved the dry state clumps of Pemulen®, but the "fish eyes" remained. It was concluded that this would not be a suitable method of manufacture for the gel, so the manufacture was discontinued without addition of the AMP. This example demonstrates the need to prepare the minoxidil solution and Pemulen® dispersion separately.

5 **Example IV**

A 5% minoxidil gel was prepared as follows:

Part I Solution

Minoxidil USP	175 g
Propylene Glycol USP	1.75 kg
Alcohol USP	770 g
DIPA	17.5 g

Part II Dispersion

Carbopol® 934P	17.5 g
Purified Water USP	770 g

Procedure

The Part II dispersion was very thick and doughy, and was unacceptable for use in planetary mixers commonly used for gel manufacturing. A further attempt was made using differing ratios of water and alcohol in the Part II dispersion without improvement. In both cases, the combination of Part I with Part II resulted in precipitation of both the minoxidil and Carbopol® 934P. This example demonstrates that the gels of the present invention cannot be made by using Carbopol® 934P as the thickening agent.

Example V

A gel composition containing 5% minoxidil was prepared as follows:

Part I Solution

Minoxidil USP	50.7 mg
Propylene Glycol USP	473 mg
Alcohol USP	130 mg

AMP-95® (2-amino- 2-methyl-1-propanol)	3 mg
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Part II Dispersion

Pemulen® TR-1 NF	5 mg
Propylene Glycol USP	52.6 mg
Purified Water USP	153 mg
Alcohol USP	130 mg

Procedure

The Part I propylene glycol, alcohol and minoxidil were combined at room temperature and mixed. After a suitable mixing period, the minoxidil had failed to dissolve so the propylene glycol intended for Part II was added to Part I. The Part II dispersion was then prepared as described in Example I. The gel manufacture was completed as described in Example I. The resultant gel was comparable to that of Example I. This example demonstrates the importance of adding the entire quantity of propylene glycol to Part I.

Example VI

A gel composition within the scope of the present invention and containing 5% minoxidil was prepared as follows:

Part I Solution

Minoxidil USP	50.7 mg
Propylene Glycol USP	526 mg
Alcohol USP	130 mg
Diisopropanolamine (DIPA)	1.5 mg

Part II Dispersion

Carbopol® 981 NF	4.0 mg
Purified Water USP	153 mg
Alcohol USP	134.8 mg

Procedure

The alcohol and propylene glycol in Part I were mixed together, and the minoxidil was dissolved in the resulting solvent mixture. Diisopropanolamine (DIPA) was added to the solution and mixed until dissolved. The alcohol and water in Part II were combined. The Carbopol® 981 NF was gradually mixed into the alcohol/water mixture, until a uniform dispersion was produced. The Part I solution was then gradually added to the Part II dispersion with constant mixing, until a uniform gel developed. The resulting gel had a very nice appearance, with a smooth consistency, excellent clarity and a moderate viscosity. This example demonstrates that the gel can be made with solvent-tolerant carbomers and alternate neutralizing agents.

Example VII

A gel composition within the scope of the present invention and containing 5% minoxidil was prepared as follows:

Part I Solution

Minoxidil USP	50.7 mg
Propylene Glycol USP	526 mg
Alcohol USP	130 mg
AMP-95® (2-amino-2-methyl-1-propanol)	1.5 mg

Part II Dispersion

Carbopol® Ultrez™ 10	2.5 mg
Purified Water USP	153 mg
Alcohol USP	136.3 mg

Procedure

The alcohol and propylene glycol in Part I were mixed together, and the minoxidil was dissolved in the resulting solvent mixture. AMP-95® was added to the solution and mixed until dissolved. The alcohol and water in Part II were combined. The Ultrez™ 10 was gradually mixed into the alcohol/water mixture, until a uniform dispersion was produced. The Part I

solution was then gradually added to the Part II dispersion with constant mixing, until a uniform gel developed. The resulting gel had a very nice appearance, with a smooth consistency, excellent clarity and a high viscosity. This example demonstrates that a variety of solvent-tolerant carbomers can be used to produce a broad range of viscosities.

5 **Example VIII**

A gel composition within the scope of the present invention and containing 5% minoxidil was prepared as follows:

Minoxidil USP	50.7 mg
Propylene Glycol USP	526 mg
Alcohol USP	260.3 mg
Purified Water USP	153 mg
Hydroxypropyl cellulose NF	10 mg

Procedure

10 The propylene glycol, alcohol, water and minoxidil were combined and mixed together until the minoxidil was dissolved. The hydroxypropyl cellulose was gradually mixed into the minoxidil solution until a uniform gel was produced. The resulting gel was clear and air-free with a moderate viscosity. This example demonstrates the use of non-carbomeric thickening agents and a suitable alternate method of manufacture.

20 The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in their entirety.

Various modification of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed is:**CLAIMS**

- 5 1. A composition comprising minoxidil, a non-carbomeric thickening agent, and a pharmaceutically acceptable solvent, wherein said minoxidil is substantially solubilized in said composition.
2. A composition of claim 1, wherein said composition is in the form of a gel.
3. A composition of claim 1 which comprises from greater than about 0.01% to about 8% minoxidil.
- 10 4. A composition of claim 3 which comprises from greater than about 3% to about 8% minoxidil.
5. A composition of claim 4 which comprises from about 5% to about 6% minoxidil.
6. A composition of claim 5 which comprises about 5% minoxidil.
- 15 7. A composition of claim 1, wherein said pharmaceutically acceptable solvent is selected from the group consisting of alcohols and polyols.
8. A composition of claim 7, wherein said solvent comprises an alcohol.
9. A composition of claim 8, wherein said alcohol is selected from the group consisting of ethanol, propanol, and butanol.
- 20 10. A composition of claim 9, wherein said alcohol is selected from the group consisting of ethanol and isopropanol.

11. A composition of claim 7, wherein said solvent comprises a polyol.

12. A composition of claim 11, wherein said polyol comprises a glycol.

13. A composition of claim 12, wherein said glycol is selected from the group consisting of propylene glycol, dipropylene glycol, hexylene glycol, 1,3-butylene glycol, PEG-
5 200, PEG-400, and glycerol.

14. A composition of claim 13, wherein said glycol is propylene glycol.

15. A composition of claim 7, wherein said solvent comprises a mixture of an alcohol and a glycol.

16. A composition of claim 15, wherein said solvent comprises a mixture of ethanol and propylene glycol.

17. A composition of claim 1, further comprising a neutralizing agent.

18. A composition of claim 17, wherein said neutralizing agent is selected
15 from the group consisting of ammonium hydroxide, arginine, 2-amino-2-methyl-1-propanol, dimethanolamine, dibutanolamine, diisobutanolamine, tributanolamine, triisobutanolamine, tri-sec-butanolamine, tripropylamine, ethanolamine, diethanolamine, triethanolamine, PEG-15 cocamine, diisopropanolamine, methylethanolamine, diisopropylamine, dipropylenetriamine, tromethamine, isopropylamine ethylene diamine, triisopropanolamine, tetrahydroxypropyl
20 ethylenediamine, trimethamine, 2-aminobutanol, aminoethyl propanediol, aminomethyl propanediol, aminomethyl propanol, sodium hydroxide, and potassium hydroxide.

19. A composition of claim 18, wherein said neutralizing agent is selected from the group consisting of 2-amino-2-methyl-1-propanol, diisopropanolamine, triisopropanolamine, and tetrahydroxypropyl ethylenediamine.

20. A composition of claim 19, wherein said neutralizing agent is 2-amino-2-methyl-1-propanol.

21. A composition of claim 1, wherein said solvent is present in said composition in an amount of at least about 20%.

5 22. A composition of claim 21 which comprises from about 20% to about 99% solvent.

10 23. A composition of claim 1, further comprising pharmaceutically acceptable additives and ingredients selected from the group consisting of hair conditioners, panthenol derivatives, calcium pantothenate, colorants, fragrances, fragrance modifiers, vitamin E, penetration modifiers, surfactants, cosmetic agents, fatty acids and fatty acid esters, herbal extracts, henna, oils, emulsifiers, wetting agents, sunscreens, and anti-irritants.

15 24. A composition of claim 1, wherein said non-carbomeric thickening agent is selected from the group consisting of organic thickening agents and inorganic thickening agents.

25. A composition of claim 24, wherein said non-carbomeric thickening agent comprises an organic thickening agent which is a polymer.

26. A composition of claim 25, wherein said polymer is selected from the group consisting of starches, gums, pectin, casein, gelatin, phycocolloids, and synthetic polymers.

20 27. A composition of claim 26, wherein said polymer is selected from the group consisting of alginates and salts and derivatives thereof, acacia, carrageenan, guar gum, karaya gum, locust bean gum, tragacanth, xanthan gum, carboxymethylcellulose and salts thereof, ethylcellulose, hydroxyethylcellulose, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, cellulose, hyaluronic acid and salts thereof, and polydextrose.

28. A composition of claim 27, wherein said polymer is selected from the group consisting of crosslinked copolymers of acrylic acid, dimethicone copolyols, acrylic/acrylate copolymers, polyacrylamide, ethylene/sodium acrylate copolymer, acrylamide/sodium acrylate copolymer, sodium acrylate/vinyl alcohol copolymer, sodium
5 polymethacrylate, sodium polystyrene sulfonate, povidone and derivatives thereof, polyquaternium compounds, polyvinyl alcohol, polyethylene oxide, and poloxamers.

29. A composition of claim 28, wherein said polymer comprises a crosslinked copolymer of acrylic acid.

10 30. A composition of claim 29, wherein said crosslinked copolymer of acrylic acid comprises an acrylate/C₁₀₋₃₀ alkyl acrylate crosspolymer.

31. A composition of claim 24, wherein said thickening agent comprises an inorganic thickening agent.

15 32. A composition of claim 31, wherein said inorganic thickening agent is selected from the group consisting of bentonite, magnesium aluminum silicate, and colloidal silicon dioxide.

33. A composition of claim 2, wherein said thickening agent comprises a crosslinked copolymer of acrylic acid.

34. A composition of claim 33, wherein said crosslinked copolymer of acrylic acid comprises an acrylate/C₁₀₋₃₀ alkyl acrylate crosspolymer.

20 35. A composition of claim 33 wherein said solvent is present in said composition in an amount of at least about 20%.

36. A composition comprising greater than 3% minoxidil, a pharmaceutically acceptable solvent, and a solvent-tolerant carbomer, wherein said minoxidil is substantially solubilized in said composition.

5 37. A composition of claim 36 which is in the form of a gel.

38. A composition of claim 36 which comprises from greater than 3% to about 8% minoxidil.

39. A composition of claim 38 which comprises from about 4% to about 7% minoxidil.

10 40. A composition of claim 39 which comprises from about 5% to about 6% minoxidil.

41. A composition of claim 40 which comprises about 5% minoxidil.

42. A composition of claim 37 wherein said pharmaceutically acceptable solvent is selected from the group consisting of alcohols and polyols.

15 43. A composition of claim 42, wherein said solvent comprises an alcohol.

44. A composition of claim 43, wherein said alcohol is selected from the group consisting of ethanol, propanol, and butanol.

45. A composition of claim 44, wherein said alcohol is selected from the group consisting of ethanol and isopropanol.

20 46. A composition of claim 42, wherein said solvent comprises a polyol.

47. A composition of claim 46, wherein said polyol comprises a glycol.

48. A composition of claim 47, wherein said glycol is selected from the group consisting of propylene glycol, dipropylene glycol, hexylene glycol, 1,3-butylene glycol, PEG-200, PEG-400, and glycerol.

49. A composition of claim 48, wherein said glycol is propylene glycol.

50. A composition of claim 49, wherein said solvent comprises a mixture of an alcohol and a glycol.

51. A composition of claim 50, wherein said solvent comprises a mixture of ethanol and propylene glycol.

52. A composition of claim 37, further comprising a neutralizing agent.

53. A composition of claim 52, wherein said neutralizing agent is selected from the group consisting of arginine, 2-amino-2-methyl-1-propanol, dimethanolamine, dibutanolamine, diisobutanolamine, tributanolamine, triisobutanolamine, tri-sec-butanolamine, tripropylamine, ethanolamine, diethanolamine, triethanolamine, PEG-15 cocamine, diisopropanolamine, methylethanolamine, diisopropylamine, dipropylenetriamine, tromethamine, isopropylamine ethylene diamine, triisopropanolamine, tetrahydroxypropyl ethylenediamine, trimethamine, 2-aminobutanol, aminoethyl propanediol, aminomethyl propanediol, and aminomethyl propanol.

54. A composition of claim 53, wherein said neutralizing agent is selected from the group consisting of 2-amino-2-methyl-1-propanol, diisopropanolamine, triisopropanolamine, and tetrahydroxypropyl ethylenediamine.

55. A composition of claim 54, wherein said neutralizing agent is 2-amino-2-methyl-1-propanol.

56. A composition of claim 37, wherein said solvent is present in said composition in an amount of at least about 20%.

57. A composition of claim 56 which comprises from about 20% to about 99% solvent.

58. A composition of claim 57 wherein the ratio of solvent to minoxidil is about 10:1.

59. A composition of claim 58 wherein the ratio of solvent to minoxidil is about 12:1.

60. A composition of claim 59 wherein the ratio of solvent to minoxidil is about 15:1.

61. A composition of claim 37, further comprising pharmaceutically acceptable additives and ingredients selected from the group consisting of hair conditioners, panthenol derivatives, calcium pantothenate, colorants, fragrances, fragrance modifiers, vitamin E, penetration modifiers, surfactants, cosmetic agents, fatty acids and fatty acid esters, herbal extracts, henna, oils, emulsifiers, wetting agents, sunscreens, and anti-irritants.

62. A composition comprising:
from greater than about 3% to about 8% of minoxidil;
from about 30% to about 80% of a polyol;
from about 10% to about 50% of an alcohol;
from about 0.01% to about 50% of a non-carbomeric polymer;
from about 0% to about 3% of a neutralizing agent; and
water (qs); wherein said minoxidil is substantially solubilized in said composition.

63. A composition of claim 62 which is in the form of a gel.

64. A composition of claim 62, wherein said polyol comprises a glycol.

65. A composition of claim 64, wherein said glycol is selected from the group consisting of propylene glycol, dipropylene glycol, hexylene glycol, 1,3-butylene glycol, PEG-200, PEG-400, and glycerol.

5 66. A composition of claim 65, wherein said glycol is propylene glycol.

67. A composition of claim 62, wherein said alcohol is selected from the group consisting of ethanol, propanol, and butanol.

68. A composition of claim 67, wherein said alcohol is selected from the group consisting of ethanol and isopropanol.

10 69. A composition of claim 62, wherein said non-carbomeric thickening agent comprises a crosslinked copolymer of acrylic acid.

70. A composition of claim 69 wherein said crosslinked copolymer of acrylic acid comprises an acrylate/C₁₀₋₃₀ alkyl acrylate crosspolymer.

15 71. A composition of claim 62, wherein said neutralizing agent is selected from the group consisting of arginine, 2-amino-2-methyl-1-propanol, dimethanolamine, dibutanolamine, diisobutanolamine, tributanolamine, triisobutanolamine, tri-sec-butanolamine, tripropylamine, ethanolamine, diethanolamine, triethanolamine, PEG-15 cocamine, diisopropanolamine, methylethanolamine, diisopropylamine, dipropylenetriamine, tromethamine, isopropylamine ethylene diamine, triisopropanolamine, tetrahydroxypropyl ethylenediamine,
20 trimethamine, 2-aminobutanol, aminoethyl propanediol, aminomethyl propanediol, and aminomethyl propanol.

72. A composition of claim 71, wherein said neutralizing agent is selected from the group consisting of 2-amino-2-methyl-1-propanol, diisopropanolamine, triisopropanolamine, and tetrahydroxypropyl ethylenediamine, and mixtures thereof.

73. A composition of claim 72, wherein said neutralizing agent is 2-amino-2-methyl-1-propanol.

74. A composition of claim 62, comprising:
from about 4% to about 7% of minoxidil;
from about 40% to about 70% of a polyol;
from about 20% to about 30% of an alcohol;
from about 0.05% to about 3% of a non-carbomeric polymer; and
from about 0.03% to about 1% of a neutralizing agent.

75. A composition of claim 74, comprising:
from about 5% to about 6% of minoxidil;
from about 50% to about 60% of a polyol; and
from about 25% to about 30% of an alcohol.

76. A composition of claim 74 comprising:
about 5% of minoxidil;
about 53% of a polyol;
about 26% of an alcohol;
from about 0.25% to about 1% of a non-carbomeric polymer; and
from about 0.15% to about 0.6% of a neutralizing agent.

77. A composition of claim 62, wherein said non-carbomeric polymer is selected from the group consisting of alginates and salts and derivatives thereof, acacia, carrageenan, guar gum, karaya gum, locust bean gum, tragacanth, xanthan gum, carboxymethylcellulose and salts thereof, ethylcellulose, hydroxyethylcellulose, methylcellulose,

hydroxypropyl cellulose, hydroxypropyl methylcellulose, cellulose, hyaluronic acid and salts thereof, and polydextrose.

5 78. A composition of claim 62, wherein said non-carbomeric polymer is selected from the group consisting of crosslinked copolymers of acrylic acid, dimethicone copolyols, acrylic/acrylate copolymers, polyacrylamide, ethylene/sodium acrylate copolymer, acrylamide/sodium acrylate copolymer, sodium acrylate/vinyl alcohol copolymer, sodium polymethacrylate, sodium polystyrene sulfonate, povidone and derivatives thereof, polyquaternium compounds, polyvinyl alcohol, polyethylene oxide, and poloxamers.

10 79. A non-gelled composition comprising minoxidil, a thickening agent, and a pharmaceutically acceptable solvent, wherein said minoxidil is substantially solubilized in said composition.

80. A composition of claim 79 which comprises from about 0.01 to about 8% minoxidil.

15 81. A composition of claim 79, wherein said thickening agent is selected from the group consisting of organic thickening agents and inorganic thickening agents.

82. A composition of claim 81, wherein said thickening agent comprises an organic thickening agent which is a polymer.

20 83. A composition of claim 82, wherein said polymeric thickening agent is selected from the group consisting of starches, gums, pectin, casein, gelatin, phycocolloids and synthetic polymers.

84. A composition of claim 83, wherein said polymeric thickening agent is selected from the group consisting of alginates and salts and derivatives thereof, acacia, carrageenan, guar gum, karaya gum, locust bean gum, tragacanth, xanthan gum, carboxymethylcellulose and salts thereof, ethylcellulose, hydroxyethylcellulose, methylcellulose,

hydroxypropyl cellulose, hydroxypropyl methylcellulose, cellulose, hyaluronic acid and salts thereof, and polydextrose.

5 85. A composition of claim 83, wherein said polymeric thickening agent is selected from the group consisting of crosslinked homopolymers of acrylic acid, crosslinked copolymers of acrylic acid, crosslinked interpolymers of acrylic acids, dimethicone copolyols, acrylic/acrylate copolymers, polyacrylamide, ethylene/sodium acrylate copolymer, acrylamide/sodium acrylate copolymer, sodium acrylate/vinyl alcohol copolymer, sodium polymethacrylate, sodium polystyrene sulfonate, povidone and derivatives thereof, polyquaternium compounds, polyvinyl alcohol, polyethylene oxide, and poloxamers.

10 86. A composition of claim 85, wherein said polymeric thickening agent comprises a crosslinked copolymer of acrylic acid.

87. A composition of claim 86, wherein said crosslinked copolymer of acrylic acid comprises an acrylate/C₁₀₋₃₀ alkyl acrylate crosspolymer.

15 88. A composition of claim 81, wherein said thickening agent comprises an inorganic thickening agent.

89. A composition of claim 88, wherein said inorganic thickening agent is selected from the group consisting of bentonite, magnesium aluminum silicate, and colloidal silicon dioxide.

20 90. A composition of claim 79, wherein said pharmaceutically acceptable solvent is selected from the group consisting of an alcohol and a polyol.

91. A composition of claim 90, wherein said solvent comprises an alcohol.

92. A composition of claim 91, wherein said alcohol is selected from the group consisting of ethanol, propanol, and butanol.

93. A composition of claim 92, wherein said alcohol is selected from the group consisting of ethanol and isopropanol.

94. A composition of claim 90, wherein said solvent comprises a polyol.

95. A composition of claim 94, wherein said polyol comprises a glycol.

5 96. A composition of claim 95, wherein said glycol is selected from the group consisting of propylene glycol, dipropylene glycol, hexylene glycol, 1,3-butylene glycol, PEG-200, PEG-400, and glycerol.

97. A composition of claim 96, wherein said glycol is propylene glycol.

98. A composition of claim 79, further comprising a neutralizing agent.

10 99. A composition of claim 98, wherein said neutralizing agent is selected from the group consisting of ammonium hydroxide, arginine, 2-amino-2-methyl-1-propanol, dimethanolamine, dibutanolamine, diisobutanolamine, tributanolamine, triisobutanolamine, tri-sec-butanolamine, tripropylamine, ethanolamine, diethanolamine, triethanolamine, PEG-15 cocamine, diisopropanolamine, methylethanolamine, diisopropylamine, dipropylenetriamine, tromethamine, isopropylamine ethylene diamine, triisopropanolamine, tetrahydroxypropyl ethylenediamine, trimethamine, 2-aminobutanol, aminoethyl propanediol, aminomethyl propanediol, aminomethyl propanol, sodium hydroxide, and potassium hydroxide.

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20 100. A composition of claim 99, wherein said neutralizing agent is selected from the group consisting of 2-amino-2-methyl-1-propanol, diisopropanolamine, triisopropanolamine, and tetrahydroxypropyl ethylenediamine.

101. A composition of claim 100, wherein said neutralizing agent is 2-amino-2-methyl-1-propanol.

102. A composition of claim 79, wherein said solvent is present in said composition in an amount of at least about 20%.

103. A composition of claim 102 which comprises from about 20% to about 99% solvent.

5 104. A composition of claim 79, further comprising pharmaceutically acceptable additives and ingredients selected from the group consisting of hair conditioners, panthenol derivatives, calcium pantothenate, colorants, fragrances, fragrance modifiers, vitamin E, penetration modifiers, surfactants, cosmetic agents, fatty acids and fatty acid esters, herbal extracts, henna, oils, emulsifiers, wetting agents, sunscreens, and anti-irritants.

10 105. A process for preparing a composition comprising:
from greater than about 3% to about 8% of minoxidil;
from about 30% to about 80% of a polyol;
from about 10% to about 50% of an alcohol;
from about 0.01% to about 3% of a non-carbomeric polymer;
15 from about 0% to about 3% of a neutralizing agent; and
water (qs); wherein said minoxidil is substantially solubilized in said composition, said process comprising:

20 (a) providing a solution comprising said minoxidil, said polyol, a portion of said alcohol, and a substantial majority of said neutralizing agent;

(b) providing a dispersion comprising said polymeric thickening agent, the remaining portion of said alcohol, any remainder of said neutralizing agent and said water; and

25 (c) combining said solution and said dispersion to provide said composition.

106. A process according to claim 105, wherein said portion of said alcohol comprises about 50% of said alcohol.

107. A process according to claim 105 comprising mixing together said minoxidil, said polyol, said alcohol and said neutralizing agent to provide said solution.

108. A process according to claim 107, wherein said mixing is conducted at about room temperature.

5 109. A process according to claim 105, wherein said neutralizing agent is substantially completely added to said solution.

10 110. A process for preparing a non-gelled composition comprising minoxidil, a thickening agent, a pharmaceutically acceptable solvent, and water, wherein said minoxidil is substantially solubilized in said non-gelled composition, said process comprising combining together said minoxidil, thickening agent, pharmaceutically acceptable solvent and water to provide said composition.

111. A method for treating or preventing hair loss in a region of a patient, said method comprising topically administering to said region a composition according to claim 1.

15 112. A method according to claim 111, wherein said hair loss comprises androgenetic alopecia, frontal hair loss, bitemporal recession, vertex balding, mid-anterior balding, alopecia areata, anagen hair loss, diffuse alopecia, and telogen effluvium.

113. A method for treating or preventing hair loss in a region of a patient, said method comprising topically administering to said region a composition according to claim 37.

20 114. A method according to claim 113, wherein said hair loss comprises androgenetic alopecia, frontal hair loss, bitemporal recession, vertex balding, mid-anterior balding, alopecia areata, anagen hair loss, diffuse alopecia, and telogen effluvium.

115. A method for treating or preventing hair loss in a region of a patient, said method comprising topically administering to said region a composition according to claim 62.

116. A method according to claim 115, wherein said hair loss comprises androgenetic alopecia, frontal hair loss, bitemporal recession, vertex balding, mid-anterior balding, alopecia areata, anagen hair loss, diffuse alopecia, and telogen effluvium.

117. A method for treating or preventing hair loss in a region of a patient, said
5 method comprising topically administering to said region a composition according to claim 79.

118. A method according to claim 117, wherein said hair loss comprises androgenetic alopecia, frontal hair loss, bitemporal recession, vertex balding, mid-anterior balding, alopecia areata, anagen hair loss, diffuse alopecia, and telogen effluvium.

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ABSTRACT

NOVEL COMPOSITIONS OF MINOXIDIL

Novel compositions comprising minoxidil, a thickening agent, and a pharmaceutically acceptable solvent are presented. Also presented is a process for making a novel gel composition comprising minoxidil, and methods for using the novel compositions for treating and preventing hair loss in a region of a patient.

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